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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,627	10/08/2003	Carl H. June	WYS-01402	7408

25181 7590 12/12/2008

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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
12/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/681,627	JUNE, CARL H.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08-29-2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,7-15,17-19 and 21-45* is/are pending in the application.

4a) Of the above claim(s) *10-14,18,21 and 23-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,7-9,15,17,19 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08-29-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Status of claims. Claims 1, 3, 7-15, 17-19 and 21-45 are currently pending. Claims 10-14, 18, 21 and 23-45 were previously withdrawn form consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claims. This application contains claims 10-14, 18, 21 and 23-45 drawn to an invention nonelected with traverse in the reply filed on 10-30-2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01

3. Note that claims 3 and 7, which depend on claim 1, where inadvertently left out of the rejection of claims 1, 3, 7, 15, 17, 19 and 22 under 35 U.S.C. 112, first paragraph, in the office action filed on 05-29-2008. Accordingly, claims 3 and 7 are newly rejected under 35 U.S.C. 112, first paragraph.

4. Therefore, claims 1, 3, 7-9, 15, 17, 19 and 22 are currently under examination to which the following grounds of rejection are applicable.

Withdrawn objections in response to Applicant arguments or amendments

Cross-Reference to Related Application.

In response to Applicant's amendment of the specification to reflect the status of the now U. S. Patent No. 6,632,789 corresponding to U.S. application Serial No. 08/245,282, filed April 29, 1994, the objection to the specification has been withdrawn.

Rejections maintained in response to Applicant arguments or amendments.

Claim Rejections - 35 USC § 102(e)

To the extent that the invention embraces methods for **inhibiting T cell activation** comprising contacting the T cells with a phosphtidylinoistol 3-kinase inhibitor that inhibits PI3K in the T cell, the following rejection applies.

Claims 1, 3 and 22 remain rejected under 35 U.S.C. 102(e) as being anticipated by Bonjouklian et al., U.S. Patent No. 5,504,103, Date of Publication, April 2 1996 (hereafter referred to as Bonjouklian et al.).

Response to Applicant Arguments as they apply to rejection of Claims 1, 3 and 22 under 35 U.S.C. 35 U.S.C. 102(e)

At page 7 of Remarks, Applicants argue, "While the Examiner contends that, "it is inherent in the methods taught by Bonjouklian et al., that the administration...results in the inhibition of phosphatidylinositol-3-kinase" (p. 3 of instant Office Action), it is not inherent that such inhibition also inhibits T cell activation and production of IL-2 by a T cell. For instance, Harada et al. in 2001 (submitted herein in a Supplemental IDS), well after the priority and filing dates of both the instant application or Bonjouklian et al., state "[t]he role of PI3K in CD28 costimulation remains controversial...we conclude that PI3K is not absolutely required for CD28-mediated IL-2 gene transcription" (p. 9006, right col., 1st paragraph). They further state, "it was reported that wortmannin treatment did not decrease or, in some cases, even increased CD28-dependent co-stimulation of IL-2 production" (p. 9006, fight col., 2nd paragraph). It is clear from Harada et al., that the state of the art well after the filing of the instant application and Bonjouklian et al., was that of uncertainty and ambiguity. Contrary to the Examiner's position,

Bonjouklian et al., would not have inherently obtained an inhibition of T cell activation" [emphasis added]. Such is not persuasive.

As stated in the previous office filed on 01-18-2008, the present invention is drawn to methods of inhibition of T cell response in a subject in need of comprising contacting the T cell with an agent that inhibits phosphatidylinositol 3-kinase (P13K) and thus production of IL-2 by T cell. Claim 3 further limits the invention to an inhibitor of phosphatidylinositol-3-kinase, e.g., wortmannin. Note that the only active method step in the claims is the step of contacting a T cell with an agent such as wortmannin. Bonjouklian et al., teaches methods of treating phosphatidylnositos-3-kinase dependent conditions in a mammal comprising contacting cells with wortmannin or wortmannin analog (see col. 14-16, claims 1-20, for example) which read on the same step claimed in the method of the instant invention. Preferred embodiments of Bonjouklian et al. include treatment of diseases such as inflammation (e.g., allergies) associated with abnormal enhanced immune response. Tough Bonjouklian et al., does not specifically teach contacting T cells, T cells are abundantly present in mammals and inherently express phosphatidylinositol 3-kinase. This finding is supported by the applicant disclosure in Figures 3, 4, 7a and 7b that contacting CD28 positive T cells with wortmannin results in inhibition of phosphatidylinositol 3-kinase. As it is clear that T cells express phosphatidylinositol 3-kinase, it is inherently in the cells of a mammal in the *in vivo* method taught by Bonjouklian et al, that any contacting of the cells with wortmannin, e.g., an agent inhibiting phosphatidylinositol 3-kinase, as instantly claimed, inherently would inhibits phosphatidylinositol 3-kinase in the T cells present in that mammal. The structural limitation of wortmannin in the Bonjouklian et al, patent and the wortmannin claimed in the instant invention are the same. Furthermore, the inhibition of

phosphatidylinositol 3-kinase in T cells necessarily and inherently results in a change in cellular activities dependant on phosphatidylinositol 3-kinase, such as proliferation and lymphokine production (e.g., inhibition, activation). The prior art of Harada et al., referred by Applicants, merely discloses the binding site of phosphatidylinositol 3-kinase to the nested YMNM motif of the CD28 cytoplasmic domain. Harada further demonstrates that in the context of the association of phosphatidylinositol 3-kinase with YMNM motif, phosphatidylinositol 3-kinase acts as a negative mediator in the CD-28 mediated IL-2 gene transcription (Abstract; p. 9005, col. 2, last paragraph). Hence, any contacting of the cells with wortmannin, e.g., an agent inhibiting phosphatidylinositol 3-kinase, would inevitably and inherently have the same physiological response in both the Harada et al., publication and the instant claims, **e.g.,** phosphatidylinositol 3-kinase when associated with the YMNM motif may act as a negative mediator of CD28-mediated IL-2 gene transcription. As such the reference of Harada et al., disclosed by Applicants as extrinsic evidence to the missing of inherently contacting T cells in the method of Bonjouklian et al., would not have been recognized by persons of ordinary skill as teaching away from the claimed invention. Note that Applicants assertion, "[t]he role of PI3K in CD28 costimulation remains controversial...we conclude that PI3K is not absolutely required for CD28-mediated IL-2 gene transcription" (p. 9006, right col., 1st paragraph) is not on point as PI3K is required for the claimed IL-2 gene transcription in the invention. The Harada publication clearly supports a direct negative correlation of PI3K and IL-2 in the context of CD28-costimulation. For example, Harada evidences that only in the context of PI3K binding to the CD28 cytoplasmic domain YMNM, IL-2 promoter activation and thus gene transcription is completely abrogated (e.g., mutation Asn191 completely abolished CD28-mediated signaling) . However, when there is

disruption of the PI3K binding to the CD28 cytoplasmic domain, CD-28-mediated IL-2 gene transcription is still observed (p. 9006, col. 2, paragraph 1). Also note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. Atlas Powder Co. v. IRECO, Inc., 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999).

Claim Rejections - 35 USC § 112 - enablement

To the extent that claims 1, 3, 7, 15, 17, 19 and 22 broadly embrace an *in vivo* method of treating a human subject suffering from an autoimmune condition comprising inducing unresponsiveness to an antigen in a T cell wherein the antigen is an autoantigen so as to treat an inappropriate immune response against its own tissues, the following rejection applies.

Claims 1, 3, 7, 15-17, 19-20 and 22 remain rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for:

An *in vitro* method for inhibiting T cell activation as assessed by production of IL-2 comprising stimulating a T cell through the TCR/CD3 complex and CD28 and further contacting said T cell with an agent wherein the agent is selected from the group consisting of Wortmannin, quercetin and LY294002, thereby inhibiting the activity of phosphatidylinositol 3-kinase within the T cell,

does not reasonably provide enablement for claims directed to a method of inducing unresponsiveness to an antigen in a T cell with the intended use of treating a human subject suffering from an autoimmune disease.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Response to Applicant Arguments as they apply to rejection of Claims 1, 15, 17, 19 and 22 remain under 35 U.S.C. 112, first paragraph

At page 8 of remarks, Applicants request clarification as to why Claim 1 was rejected under 35 U.S.C. § 112, first paragraph and make note that Claim 1 was not rejected under 35 U.S.C. § 112, first paragraph, in the Final Office Action mailed December 13, 2007.

Claim 1 was included in the rejection of claims 1, 15, 17, 19 and 22 under 35 U.S.C. 112, first paragraph in the office action mailed on 05-29-2008, to the extent that claim 1 reads on an *in vivo* method of inhibiting T cell activation in a subject in need thereof as the contemplated treatment and/or prevention of an autoimmune disorder.

At page 8 of Remarks, Applicants allege, "A costimulatory signal is also required (such as CD28) or T cell receptor signaling can induce a state of anergy. Provided this and the teachings of the instant application, one of ordinary skill would only have to perform routine experimentation to practice the invention. For instance, p. 9, lines 4-13 of the instant specification teaches induction of T cell unresponsiveness to an antigen or alloantigen. Immediately following this paragraph, the specification teaches induction of T cell unresponsiveness to an antigen in vivo (p. 9, lines 14-31). Given the in vitro data and results, including from Examples 1, 2 and 5 (pages 14-17, 18-19), only routine experimentation would

be required for treating an autoimmune disease by administering T cells to a subject". Such is not persuasive.

The Examiner agrees with Applicants that peripheral tolerance distinguish between TCR engagements by foreign antigens delivered by costimulatory signals by APC but not tissue cells. Moreover, T cell activation involves stimulation of the antigen receptor (TCR) which delivers the primary stimulus and costimulation by other accessory molecules including CD28 expressed on resting T cells which bind their specific by their natural ligands leading to T cell proliferation. The instant specification contemplates at page 9, lines 14-37 bridging to page 10, lines 1-10, numerous autoimmune diseases where it is desirable to downmodulate an immune response by inducing T cell unresponsiveness, e.g., rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, contact dermatitis, psoriasis, systemic lupus erythematosus and others. These inflammatory and autoimmune disorders differ in etiologies and therapeutic end points. However, the as-filed application is silent about any factual data disclosing a method of treating autoimmune diseases in a subject. Thus the claimed invention is not enabling for treating autoimmune disorders as defined by any of the above diseases. Applicant's arguments are not on point as Applicants have not addressed pending enabling issues of the claimed invention related to treating an autoimmune disease. The instant claims broadly embrace treatment for a genus of autoimmune diseases in a subject including type 1 diabetes, systemic lupus erythematosus, autoimmune encephalomyelitis, Chrohn's, Multiple sclerosis. These are widely divergent autoimmune diseases in terms of their pathologic mechanisms and treatments. This complex pathogenesis is reflected in the variable response of patients to immunomodulatory therapy and the lack of an effective unique treatment reflected, for example, in the statement of Sykes et al.,

(Nature 2005, pp. 620-627) " although the prevention of autoimmunity might some day be clinical feasible, at the moment we cannot predict such a diseases accurately enough to justify the use of toxic preventive treatment. Unfortunately, animal studies show that preventing the onset of autoimmunity is much easier than reversing established disease" (p. 620, col. 2, paragraph 3). Thus, as each therapeutic approach should encompass the specifics for the human disorder being contemplated. The quantity of experimentation required to practice the methods as claimed would require the de novo determination of effective target sites, modes of delivery, safe administration of an agent that inhibits PI3K and formulations of the claimed agent to target appropriate cells and/or tissues in a subject in need of, and further whereby treatment effects are provided for the claimed abnormal immune condition. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope.

Rejection, Obviousness Type Double Patenting-

Claims 1, 3 and 7-9 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 7-10 of U.S. Patent No. 6, 632, 789. Applicants request that the Examiner hold all nonstatutory obviousness-type double patenting rejection in abeyance, until allowable subject matter is determined.

Because claims 1, 3 and 7-9 of the instant application are broadly drawn to an agent which inhibits production of D-3 phosphoinositides, claims 1, 3 and 7-9 embrace claims 1-4, 7-10 of U.S. Patent No. 6, 632, 789, which claim quercetin and LY294002 as the specific inhibitory agents of phosphatidylinositol 3-kinase. Thus claims 1-4, 7-10 of U.S. Patent No. 6, 632, 789,

are species of the claimed genus in the instant invention and anticipate the claimed genus of agents that inhibits production of D-3 phosphoinositides.

Conclusion

Claims 1, 3, 7-9, 15, 17, 19 and 22 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633